

Effects of Aqueous Plant Extract Mixtures in Combination with Honey on Wound Healing in Rats: an Animal Model

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Abstract: Wound healing activities of plant extract mixtures in combination with honey was studied on cutaneous excision wounds in rats. Three groups of male *Sprague Dawley* rats were used and all animals were experimentally wounded in the posterior neck area. Pure un-boiled honey was applied topically to wounds of Group 1 animals. Wounds of Group 2 rats were treated with honey in combination with 5% plant extract mixtures, and honey in combination with 10% plant extract mixtures was applied topically to wounds of Group 3 animals. The effects of vehicles on the rate of wound healing were assessed. Wounds treated with honey in combination with 10% plant extract mixtures were significantly ($p < 0.05$) accelerated wound healing compared to wounds treated by honey alone. These results strongly document the beneficial effects of 10% plant extract mixtures for the acceleration of wound healing process.

Key words: Honey, wounds healing, rats, persimmon, agaricus, lycium

INTRODUCTION

Burn trauma and wounds are still a major problem in developing countries, often having severe complications and involving high costs for therapy. An important aspect of the use of traditional medicinal remedies and plants in the treatment of burns and wounds is the potential to improve healing and the same time to reduce the financial burden. Several plants and herbs have been used experimentally to treat skin disorders, including wound injuries, in traditional medicine^[1-3].

The wound healing properties of honey had been well documented^[4-6]. Honey has been used topically for centuries to accelerate wound healing. It has been reported to be helpful in treating burns, decubitus ulcers, and infected wounds^[7]. *In vitro* it has been shown to have anti-bacterial and anti-fungal activity to organisms commonly infected surgical wounds^[8,9]. The wound healing properties of honey are thought to result from the debriding properties of the enzyme catalase, absorption of oedema because of honey's hygroscopic properties, its ability to promote granulation and re-epithelialization from wound edges, and its anti-microbial properties^[6,10,11].

Honey has long been used to accelerate wound healing^[7,12,13]. Existing literature attributes honey with a

number of useful properties, such as a broad-spectrum anti-microbial activity, deodorization, debriding and anti-inflammatory actions and stimulation of new tissue growth^[9,14]. Honey, for the most part, is made up of simple sugars and is an excellent source of energy. It is hyper tonic and has been shown to be sterile and highly bactericidal^[15,16]. Honey has been found, when applied locally, to reduce infection and promote wound healing^[17]. Physiological properties of honey such as hyper tonicity, low pH (3.6) and hygroscopic were thought to augment the healing process. Antibacterial effects were also attributed to these elements^[18,19]. The wound healing properties of honey have been cleansing, absorption of edema, antibacterial activity, deodorization, promotion of granulation, tissue formation, and epithelialization, and improvement of nutrition^[9,14,20].

The Basidiomycete fungus *Agaricus blazei* Murill has traditionally been used as a health food for the prevention of cancer, diabetes, hyperlipidemia, arteriosclerosis and chronic hepatitis^[21]. *Agaricus blazei* is a medically important mushroom widely eaten and prescribe and it used in the treatment of tissue inflammation and cancer in traditional Chinese medicine^[22]. Components of *A. blazei* have been demonstrated to have a wide range of immunopotentiating activities such as activation of

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complement system in human serum *in vitro*^[23]. The edible mushroom *A. blazei* is considered a healthy food in many countries after it was reported to be a source of antitumor and immunoreactive compound^[24]. A heat-labile protein has been identified in fruit bodies of edible mushroom, *A. bisporus*, which protects Raji cells against H₂O₂-induced oxidative damage to cellular DNA^[25]. Previous treatment with *A. blazei* significantly reduced DNA damage, indicating a protective effect against diethylnitrosamine-induced liver cytotoxicity/genotoxicity^[26,27]. Crude extracts from *Agaricus* presented significantly wide antimicrobial spectrum and were active against both fungus and bacteria^[28,29]. *Agaricus blazei* is an excellent source of antioxidants^[30], and antitumor effect^[21,31,32].

The crude extracts from the leaves of diospyrose species showed broad spectrum antimicrobial activities against a wide range of Gram-positive and Gram-negative bacteria, and fungal strains^[33-35], antifertility effect^[36], antihemorrhagic effect^[37], potential antitumor^[38,39], anti-inflammatory, antipyretic and analgesic^[40], Hypolipidemic^[41] and antioxidant properties^[41,42]. *Lycium* species possesses anticancer^[43], antioxidant^[44,45], and antitumor^[46].

The same mixture of plant extracts used in this study was applied as an encapsulated paste after being fermented with lactic acid bacteria for the treatment of oral recurrent aphthous ulcers in a previous study^[47].

The aim of the present study was to assess the effects of honey in combination with plant extracts mixture on the rate of wound-healing process in rats.

MATERIALS AND METHODS

Honey: Pure, unprocessed, un-boiled commercial honey obtained from the Faculty of Agriculture, University Putra Malaysia, Serdang Selangor Malaysia, was used for the present study.

Preparation of aqueous extracts: 40 g of each crude plant powder (*Agaricus blazei*, *Lycium chinense* and *diospyros lotus*) was weighed and mixed with 800ml of sterile distilled water in a conical flask in a ratio of 1:20. It was then heated and stirred on a hotplate for 3 h. After being

left to cool, the residue was removed by filtration using a mesh and filter funnel. Rotary evaporator was used to extract the filtered material. Equal weights of each plant extract were mixed thoroughly and 5 and 10% plant extracts mixed with honey (w/w).

Experimental animals: Sprague Dawley rats were obtained from the animal house, Faculty of Medicine, University of Malaya. The rats were divided randomly into 3 groups of 6 rats each. Each rat that weighed between 180 - 200 gm was housed separately (one rat per cage). The animals were left for 48 hours to acclimatize to the animal room conditions and were maintained on standard pellet diet and tap water.

Experimentally induced wounds: An area of tissue measuring 2 cm by 2 cm was excised from the nape of the neck in rats previously shaved, disinfected with 70% alcohol and injected with 1 ml of Lignocaine HCl (2%, 100 mg/5 mL), to the depth of the muscle, avoiding incision of the muscle layer itself. A fresh surgical blade was used for the perpendicular cut on each animal and tension of skin was kept constant during the procedure.

Topical application of vehicles: A thin layer of pure, un-boiled commercial honey was applied topically twice daily to animals in Group 1. Group 2 rats were treated with a thin layer honey in combination with 5% plant extract mixture (5% of plant extract mixture in honey w/w) applied topically twice as daily dressing. A thin layer of honey combined with 10% plant extract mixture (10% of plant extract mixture in honey w/w) was topically applied twice daily to Group 3 rats.

Statistical analysis of data: Results were expressed as mean±M.S.E. The statistical difference between the groups in the term of the mean rate of wound healing was calculated by using Student's t-test

RESULTS

Wounds treated with honey combined with 10% plant extract mixture showed considerable signs of dermal healing and significantly (p<0.05) healed earlier than those

Table 1: Time required for wound healing rate in experimental animals

Animal groups	No. of animals	Type of dressing	Healing time (days)
			Mean± M.S.E.
Group 1 (Control)	6	Honey alone	13.67 ^a
Group 2	6	5% plant extract + Honey	13.33 ^{ab}
Group 3	6	10% plant extract + Honey	12.67 ^b

All values are expressed as mean and± mean standard error; between groups, mean with different superscripts are significantly different (p<0.05)

treated with honey alone (Group 1) (Table 1). There were no significant differences between rats treated with honey alone and those with honey combined with 5% plant extract mixture in term of wound healing duration. In addition dermal wounds treated with honey combined with 10% plant extract mixtures were rapidly replaced by granulation tissue and advancing epithelialization, and the diameters of the wounds became narrow gradually.

DISCUSSION

The majority of the world's population relies on traditional medicine for their health care. This is also the case in the treatment of wounds. In developing countries, remedies prepared from herbal plants have been widely used for the treatment of soft tissue wounds and burns by medical personnel trained in western medicine as well as by traditional practitioners. The results of the present study showed that the usage of plant aqueous extracts in combination with honey as topical applicants of wounds dressing significantly ($p < 0.05$) accelerated wound healing compared to wounds treated with honey alone and the wounds were maintained sterile until complete healing in all animals. Similarly, topical application of honey has been recognized for a long time to be effective in controlling infection and producing a clean granulating wound bed^[4,6,48].

The wound healing properties of honey had been well documented^[7,13,20,49]. Topical application of honey has been recognized for a long time to be effective in controlling infection and producing a clean granulating wound bed. Honey acts mainly as a hyperosmolar medium and prevents bacterial growth. The high sugar content of honey renders the honey hyperosmolar. Due to this effect, it causes rapid absorption of edema fluid from the soggy weeping wounds. The viscosity of honey is high and it forms a physical barrier that prevents bacterial colonization of wounds and creating a moist environment. This appears to be helpful and accelerates wound healing^[7,9,13]. The nutrient contents of the honey such as laevulose and fructose improve local substrate supply and may help promote epithelialization^[6,49,50]. Honey seems to cause more rapid epithelialization, presumably because of antibacterial properties as compared to control. The enzyme catalase present in honey has an antioxidant property^[10,51] and thus honey may have a role as an antioxidant in thermal injury^[52,53].

The exposure of human lymphoid leukaemia Molt 4B cells to persimmon (*Diospyros*) extract led to both growth inhibition and the induction of programmed cell death (apoptosis)^[54]. Persimmon extract containing catechin compounds induce programmed cell death^[54]. Persimmon possesses hypolipidemic and antioxidant properties. These properties are attributed to a high concentration of

antioxidants such as carotenoids and polyphenols found in persimmon^[54,55].

Itoh *et al.*, (1994) demonstrated that administration of *Agaricus blazei* inhibits the growth of Meth A fibro sarcoma and *Agaricus blazei* may play a marked amplifying role in the development of delayed type hypersensitivity to tumour antigens. *Agaricus blazei* appears to manifest its antitumor activities by inducing various types of cytokines indirectly via host's immune system and it is conceivable that *Agaricus blazei* has immunostimulating effects and immunomodulatory effects^[56]. Inhibition of the tumour growth by *Agaricus blazei* may be due to activation of complement C3 and stimulation of phagocytic activity^[57]. The antitumor activity of *Agaricus blazei* is likely due to the enhancement of host defence functions^[57].

CONCLUSION

The effects of honey combined with 10% plant extract mixtures appeared to have several important properties that make it ideal as a dressing agent for wounds. We can suggest that it may be possible to use honey in combination with these plant extracts as topical application for the treatment of wounds. These plant extracts possess certain antioxidant effect. Therefore, the addition of the plant extract mixture to honey may be beneficial in the acceleration of wound healing. However, further investigations are required to elucidate their exact mechanism (s) of the wound healing activity.

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